5 Guidelines for Evaluation of Stability Data in Retest Periods

I. INTRODUCTION

This chapter describes when and how limited extrapolation can be undertaken to propose a retest period for a drug substance or shelf life for a drug product beyond the observed range of data from the long-term storage condition.

A. Background

Although the parent guideline (see Chapter 4) states that regression analysis is an acceptable approach to analyzing quantitative stability data for retest period or shelf-life estimation and recommends that a statistical test for batch poolability be performed using a level of significance of 0.25, it includes few details. In addition, the parent guideline does not cover situations in which multiple factors are involved in a full or reduced-design study.

B. Scope of the Guideline

This guideline, an annex to the parent guideline (Chapter 4), is intended to provide a clear explanation of expectations when proposing a retest period or shelf-life and storage conditions based on the evaluation of stability data for both quantitative and qualitative test attributes. This guideline outlines recommendations for establishing a retest period or shelf life based on stability data from single or multifactor and full or reduced-design studies. International Conference on Harmonisation (ICH) Guidelines Q6A and Q6B provide guidance on the setting and justification of acceptance criteria.

II. GUIDELINES

A. General Principles

The design and execution of formal stability studies should follow the principles outlined in the parent guideline. The purpose of a stability study is to establish, based on testing a minimum of three batches of the drug substance or product, a retest period or shelf life and label storage instructions applicable to all future batches manufactured and packaged under similar circumstances.

A systematic approach should be adopted in the presentation and evaluation of the stability information, which should include, as appropriate, results from the physical, chemical, biological, and microbiological tests, including those related to particular attributes of the dosage form (e.g., dissolution rate for solid oral dosage forms). Where appropriate, attention should be paid to reviewing the adequacy of the mass balance. Factors that can cause an apparent lack of mass balance should be considered; for example, the mechanisms of degradation and the stability-indicating capability and inherent variability of the analytical procedures. The degree of variability of individual batches affects the confidence that a future production batch will remain within acceptance criteria throughout its retest period or shelf life.

The recommendations in this guideline on statistical approaches are not intended to imply that use of statistical evaluation is preferred when it can be justified as being unnecessary. However, statistical analysis can be useful in the extrapolation of retest periods or shelf lives in certain situations and may be called for to verify the retest periods or shelf lives in other cases.

The basic concepts of stability data evaluation are the same for single- vs. multifactor studies and for full- vs. reduced-design studies. Data evaluation from the formal stability studies and, as appropriate, supporting data should be used to determine the critical quality attributes likely to influence the quality and performance of the drug substance or product. Each attribute should be assessed separately and an overall assessment made of the findings for the purpose of proposing a retest period or shelf life. The retest period or shelf life proposed should not exceed that predicted for any single attribute.

A flow diagram on how to analyze and evaluate long-term stability data for appropriate quantitative test attributes from a study with a multifactor full or reduced design is provided in Appendix A. The statistical method used for data analysis should consider the stability study design to provide a valid statistical inference for the estimated retest period or shelf life.

In general, certain quantitative chemical attributes (e.g., assay, degradation products, and preservative content) for a drug substance or product can be assumed to follow zero-order kinetics during long-term storage. Data for these attributes are therefore amenable to linear regression and poolability testing. Qualitative attributes are not amenable to statistical analysis and microbiological attributes, and certain quantitative attributes (e.g., pH,

dissolution) are generally not amenable to the type of statistical analysis.

B. Data Presentation

Data for all attributes should be presented in an appropriate format (e.g., tabular, graphical, narrative), and an evaluation of those data should be included in the application. If a statistical analysis is performed, the procedure used and the assumptions underlying the model should be stated and justified. A tabulated summary of the outcome of statistical analysis or graphical presentation of the long-term data should be included.

C. Extrapolation

Limited extrapolation to extend the retest period or shelf life beyond the observed range of available long-term data can be proposed in the application, particularly if no significant change is observed at the accelerated condition. Any extrapolation should take into consideration the possible worst-case situation at the time of batch release.

Extrapolation is the practice of using a known data set to infer information about future data sets. An extrapolation of stability data assumes that the same change pattern will continue to apply beyond the observed range of available long-term data. Hence, the use of extrapolation should be justified in terms of, for example, what is known about the mechanisms of degradation, the goodness of fit of any mathematical model, and the existence of relevant supporting data.

The correctness of the assumed change pattern is crucial if extrapolation beyond the available long-term data is contemplated. For example, when estimating a regression line or curve within the available data, the data themselves provide a check on the correctness of the assumed change pattern, and statistical methods can be applied to test the goodness of fit of the data to the assumed line or curve. No such internal check is available beyond the length of observed data. Thus, a retest period or shelf life granted on the basis of extrapolation should always be verified by additional long-term stability data as soon as these data become available. Care should be taken to include in the protocol for commitment batches a time point that corresponds to the extrapolated retest period or shelf life.

D. Data Evaluation for Retest Period or Shelf-Life Estimation for Drug Substances or Products Intended for "Room Temperature" Storage

A systematic evaluation of the data from formal stability studies should be performed as illustrated in this section. In general, stability data for each attribute should be assessed sequentially, beginning with significant change, if any, at the accelerated condition and, if appropriate, the intermediate condition, and progressing through the trends and variability of long-term data. The circumstances are delineated under which extrapolation of retest period or shelf life beyond the observed length of long-term data can be appropriate.

1. No Significant Change at Accelerated Condition

Where no significant change occurs at the accelerated condition, the retest period or shelf-life setting would depend on the nature of the long-term and accelerated data.

a. Long-Term and Accelerated Data Showing Little or No Change over Time and Little or No Variability

Where the long-term data and accelerated data for an attribute show little or no change over time and little or no variability, it may be apparent that the drug substance or product will remain well within its acceptance criterion for that attribute during the proposed retest period or shelf life. Under these circumstances, it is normally considered unnecessary to go through a statistical analysis, but justification for the omission should be provided. Justification can include a discussion of the mechanisms of degradation or lack of degradation, relevance of the accelerated data, mass balance, or other supporting data as defined in the parent guideline.

Extrapolation of the retest period or shelf life beyond the length of available long-term data can be proposed. A proposed retest period or shelf life up to twice the length of available long-term data can be proposed, but it should not exceed the length of available long-term data by more than 12 months.

b. Long-Term or Accelerated Data Showing Change over Time and Variability

If the long-term or accelerated data for an attribute show change over time or variability within a factor or among factors, statistical analysis of the long-term data can be useful in establishing a retest period or shelf life. Where there are considerable differences in stability observed among batches or other factors (e.g., container size or fill strength) or factor combinations (e.g., strength-by-container size or fill), the proposed retest period or shelf life should be based on the shortest period supported by the worst batch, factor, or factor combination. Alternatively, where the differences are readily attributed to a particular factor (e.g., strength), different shelf lives can be assigned to different levels within the factor (e.g., different strengths). A discussion should be provided to address the cause for the differences and the overall significance of such a difference on the product. Extrapolation beyond the length of available long-term data can be proposed; however, the

extent of extrapolation would depend on whether long-term data for the attribute are amenable to statistical analysis.

i. Data Not Amenable to Statistical Analysis (for Qualitative Attributes or Certain Quantitative Attributes)

When relevant supporting data are provided, a retest period or shelf life up to one and one-half times the length of available long-term data can be proposed, but it should not exceed the length of available long-term data by more than 6 months. Relevant supporting data include satisfactory long-term data from development batches that are made with a closely related formulation to, manufactured on a smaller scale than, or packaged in a container closure system similar to that of the primary stability batches.

ii. Data Amenable to Statistical Analysis

If a statistical analysis is not performed, the extent of extrapolation should be the same as above (i.e., when relevant supporting data are provided, a retest period or shelf life up to one and one-half times the length of available long-term data can be proposed, but it should not exceed the length of available long-term data by more than 6 months). However, if a statistical analysis is performed, it can be appropriate to propose a retest period or shelf life of up to twice the length of available long-term data when supported by the statistical analysis and supporting data, although this proposed retest period or shelf life should not exceed the length of available long-term data by more than 12 months.

2. Significant Change at Accelerated Condition

Where significant change (see below) occurs at the accelerated condition, the retest period or shelf life setting would depend on the outcome of stability testing at the intermediate condition, as well as long-term testing. The following physical changes can be expected to occur at the accelerated condition and would not be considered significant changes that call for intermediate testing if there is no other significant change (potential interaction effects should also be considered in establishing that there is no other significant change): softening of a suppository that is designed to melt at 37°C, if the melting point is clearly demonstrated, and failure to meet acceptance criteria for dissolution for 12 units of a gelatin capsule or gel-coated tablet if it can be unequivocally attributed to cross-linking. However, phase separation of semisolid dosage forms at the accelerated condition could call for testing at the intermediate condition.

a. No Significant Change at Intermediate Condition

If there is no significant change at the intermediate condition, extrapolation beyond the length of available long-term data can be proposed; however, the extent of extrapolation would depend on whether long-term data for the attribute are amenable to statistical analysis.

i. Data Not Amenable to Statistical Analysis

Based on an attribute that is not amenable to statistical analysis, a retest period or shelf life can be proposed when relevant supporting data are provided, but the proposed retest period or shelf life should not exceed the length of available long-term data by more than 3 months.

ii. Data Amenable to Statistical Analysis

If the long-term data for an attribute are amenable to statistical analysis but such an analysis is not performed, the extent of extrapolation would be the same as above. However, if a statistical analysis is performed, it can be appropriate to propose a retest period or shelf life of up to one and one-half times the length of available long-term data when supported by the statistical analysis and relevant supporting data, but not exceeding the length of available long-term data by more than 6 months.

b. Significant Change at Intermediate Condition

Where significant change occurs at the intermediate condition, the proposed retest period or shelf life should not exceed the extent of available long-term data. In addition, a shorter retest period or shelf life could be called for. If the long-term data show variability, verification of the retest period or shelf life by statistical analysis can be appropriate.

E. Data Evaluation for Retest Period or Shelf-Life Estimation for Drug Substances or Products Intended for Storage Below "Room Temperature"

1. Drug Substances or Products Intended for Refrigerated Storage

Data from products intended to be stored in a refrigerator should be assessed according to the same principles described throughout this document for the general case pertaining to products intended for "room temperature" storage, except where explicitly noted in the section below. A decision tree is provided in Appendix A as an aid to the guidance below.

a. No Significant Change at Accelerated Condition for Products Intended for Refrigerated Storage

Where no significant change occurs at the accelerated condition, extrapolation of retest period or shelf life beyond the length of available long-term data can be proposed. The proposed retest period or shelf life can be up to one and one-half times the length of available long-term data, but should not exceed the length of available long-term data by more than 6 months.

b. Significant Change at Accelerated Condition for Products Intended for Refrigerated Storage

If significant change occurs between 3 and 6 months' testing at the accelerated storage condition, the proposed retest period or shelf life should be based on the real-time data available at the long-term storage condition. No extrapolation can be considered.

If significant change occurs within the first 3 months' testing at the accelerated storage condition, the proposed retest period or shelf life should be based on the real-time data available at the long-term storage condition. No extrapolation should be performed. In addition, a discussion should be provided to address the effect of short-term excursions outside the label storage condition (e.g., during shipping or handling). This discussion can be supported, if appropriate, by further testing on a single batch of the drug substance or product for a period shorter than 3 months.

2. Drug Substances or Products Intended for Storage in a Freezer

For drug substances and products intended for storage in a freezer, the retest period or shelf life should be based on the real-time data obtained at the long-term storage condition. In the absence of an accelerated storage condition for drug substances or products intended to be stored in a freezer, testing on a single batch at an elevated temperature (e.g., 5° ± 3°C or 25° ± 2°C) for an appropriate time period should be conducted to address the effect of short-term excursions outside the proposed label storage condition (e.g., during shipping or handling).

3. Drug Substances or Products Intended for Storage Below –20°C

For drug substances and products intended for storage below –20°C, the retest period or shelf life should be based on the real-time data obtained at the proposed long-term storage condition and should be assessed on a case-by-case basis.

F. General Statistical Approaches

Where applicable, an appropriate statistical method should be employed to analyze the long-term primary stability data in an original application. The purpose of this analysis is to establish, with a high degree of confidence, a retest period or shelf life during which a quantitative attribute will remain within acceptance criteria for all future batches manufactured, packaged, and stored under similar circumstances. This same method could also be applied to commitment batches to verify or extend the originally approved retest period or shelf life.

Regression analysis is considered an appropriate approach to evaluating the stability data for a quantitative attribute and establishing a retest period or shelf life. The nature of the relationship between an attribute and time will determine whether data should be transformed for linear regression analysis. Usually the relationship can be represented by a linear or nonlinear function on an arithmetic or logarithmic scale. Sometimes a nonlinear regression can be expected to better reflect the true relationship.

An appropriate approach to retest period or shelf-life estimation is to analyze a quantitative attribute by determining the earliest time at which the 95% confidence limit for the mean around the regression curve intersects the proposed acceptance criterion.

For an attribute known to decrease with time, the lower one-sided 95% confidence limit should be compared with the acceptance criterion. For an attribute known to increase with time, the upper one-sided 95% confidence limit should be compared with the criterion. For an attribute that can either increase or decrease, or whose direction of change is not known, two-sided 95% confidence limits should be calculated and compared with the upper and lower acceptance criteria.

The statistical method used for data analysis should take into account the stability study design to provide a valid statistical inference for the estimated retest period or shelf life. The approach described above can be used to estimate the retest period or shelf life for a single batch or for multiple batches when combined after an appropriate statistical test.

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APPENDIX A: DECISION TREE FOR DATA EVALUATION FOR RETEST PERIOD OR SHELF LIFE ESTIMATION FOR DRUG SUBSTANCES OR PRODUCTS (EXCLUDING FROZEN PRODUCTS)

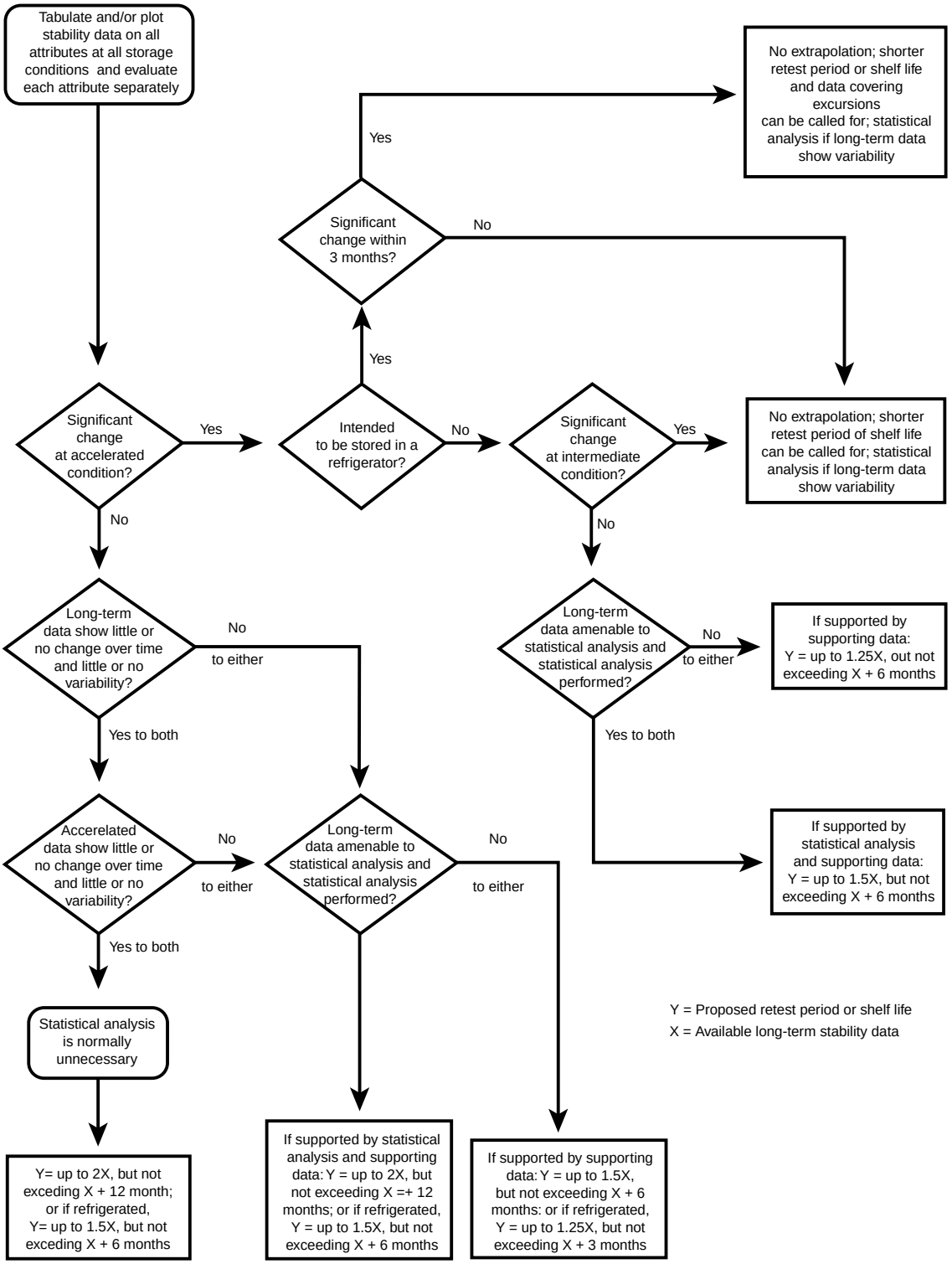

FIGURE 5.1